REMARKS

I. Claim Rejections - 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claim 21 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner argues that the limitation of claim 21, "are administered at a rate of 0.01 to 50 pmol per kg of body weight of patient per minute" constitutes new matter "to [the] extent that these recited amounts encompass parenteral administration means other than 'infusion'".

Although it is believed that the claimed dosing range inherently only describes administration by infusion, claim 21 has now been amended so that it is now explicit. The Examiner's rejection is therefore rendered moot.

II. Claim Rejections - 35 U.S.C. § 102

Claims 1-2, 17-19, 20-25, 32-35, and 41-50 were rejected under 35 U.S.C. § 102(e) as being anticipated by Habener, U.S. Pat. No. 5,614,492 ("Habener '492"). Applicants respectfully traverse this rejection.

A rejection for anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention. Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co., 730 F.2d 1452, 221 USPQ 481, 485 (Fed. Cir. 1984). Further, the reference must generally place the needed subject matter supporting the anticipation rejection in the public domain before the date of invention. In re Zenitz, 333 F.2d 924, 142 USPQ 158, 160 (C.C.P.A. 1964). It follows from this second element that a reference does not legally anticipate the claimed subject matter if it is found not to be sufficiently enabling, in other words, if it does not place the subject matter of the claims within the possession of the public. In re Wilder, 429 F.2d 447, 166 USPQ 545 (C.C.P.A. 1970).

As stated by the Examiner, Habener '492 discloses the use of GLP 1 and its derivatives to treat both diabetes and hyperglycemia due to the peptide's "insulinotropic" activity. (Col. 6, lines

1-8). Thus, Habener's method is directed only towards treating patients with these diseases for purposes of lowering their plasma glucose levels.

In contrast, claims 1-2, 17-19, 20-25, 32-35, 41, 42, 44, and new claim 51 are directed to a method "for non-alimentary nutrition" (claims 1-2, 17-19, 20-25, 32-35, and 51) and a method of "enhancing metabolism of nutrients" (claims 41-42 and 44) comprising the administration of a "nutritively effective composition" comprising one or more nutrients and insulinotropic peptides. As discussed on p. 4 of the specification, the insulinopeptides such as GLP-1 and GIP have been known for some time and, as set forth in Habener '492, their use has been directed solely to treating patients with diabetes, i.e. lowering plasma glucose. Applicants' claimed invention, however, teaches the administration of insulinotropic compounds for providing nutrition and enhancing the metabolism of nutrients in patients. Specifically, the administration of the combination of Applicants' insulinotropic peptides and nutrients may be unexpectedly used to provide high and rapid nutrition that avoids hyperglycemia, while also avoiding the dangers of hypoglycemia, even in non-diabetic patients. (Spec. p. 5). In fact, claim 32 specifically requires that the Applicants' compositions are administered to a non-diabetic patient, in direct contrast to the teachings of Habener '492.

The Examiner argues that Habener's "meal studies" as described in Example 11 anticipate the claimed invention, since such studies also involve the administration of nutrients. However, this is simply not the case since Habener's meal studies are still exclusively directed to the treatment of diabetic patients. (Col. 26, lines 19-23).

Since Habener '492 does not teach a method of using insulinotropic peptides for any purpose other than decreasing plasma glucose levels, it does not anticipate claims 1-2, 17-19, 20-25, 32-35, 41, 42, 44, and 51.

Further, Habener '492 fails to teach the co-administration of an insulinotropic peptide and a nutrient. Claims 1-2, 17-19, 20-25, 32-35, and 41-51 require the administration of "a nutritively effective amount of" one or more nutrients. This amount is defined in the specification, as well as claims 1 and 44, as providing concentrations of nutrients that are at least

the same "as that typically used for parenteral feeding and the rate of administration is at least the same but preferably higher than typically prescribed such as preferably a rate providing up to 1000 g of glucose or its equivalent per patient per day." (Spec. p. 3, lines 25-29). Claim 20 further specifies that the administration of the nutrient to the patient "produces a blood glucose level in the patient of from about 80 to 180 mg glucose per deciliter of blood".

In contrast, Habener '492 states that his GLP-1 derivatives are "substantially free of natural contaminants", which Habener defines as "other peptides, carbohydrates, glycosylated peptides, lipids, membranes, etc." (Col. 9, lines 16-23), i.e. Applicants' nutritive components. Habener further notes that a material is also said to be substantially free of natural contaminants "if these contaminants are substantially absent from a sample of material." (Col. 9, lines 23-26). Thus, Habener '492 actually teaches away from the inclusion of Applicants' nutrients in their claimed amounts. Habener '492 therefore does not anticipate claims 1-2, 17-19, 20-25, 32-35, and 41-51.

The Examiner asserts that Habener's disclosure that it is substantially free of Applicants' claimed nutrients is negated by his disclosure of "parenteral administration" of GLP 1 and its derivatives "in pharmaceutical compositions comprising carbohydrates (e.g. lactose), polyamino acids: controlled release formulations comprising lipid derivatives (e.g. liposomes) e.g. see bottom of col. 9 to top of col. 10) as well as conjugates thereof (e.g. see col. 10, lines 13-26)."

While Habener '492 teaches parenteral administration of GLP-1 derivatives, he does not teach parenteral administration of GLP-1 derivatives in combination with Applicants' claimed nutrients. Habener discloses that his parenteral compositions are administered in distilled water. (Col. 9, lines 40-44). Habener's only teaches the administration of GLP-1 derivatives in combination with carbohydrates with respect to non-parenteral pharmaceutical compositions. (See bottom of p. 9 to top of p. 10).

For instance, Habener '492 teaches the preparation of controlled release preparations by incorporating GLP-1 "into particles of a polymeric material such as polyesters, polyamino acids, hydrogels, poly (lactic acid) or ethylene vinylacetate copolymers." (Col. 9 lines 64-67 to Col. 10

lines 1-2). Habener '492 also notes that instead of incorporating GLP-1 into these polymeric materials, "it is possible to entrap these derivatives in microcapsules", such as liposomes, albumin microspheres, microemulsions, nanoparticles, and nanocapsules or in macroemulsions." (Col. 10, lines 2-12). Further, Habener '492 describes methods of enhancing the biological half-life of GLP-1 by bonding such derivatives to one or more chemical "moieties", such as lipids, carbohydrates, amino acid residues, etc. (Col. 10, lines 14-25). A person skilled in the pharmaceutical arts would understand, however, that such controlled release preparations relate primarily to non-parenteral dosage forms. This is in contrast to claims 1-2, 17-19, 20-25, 32-35, and 41-51 which all require the parenteral administration of insulinotropic peptides in combination with one or more nutrients.

Furthermore, Habener '492 does not teach the inclusion of carbohydrates and other compounds in its compositions in a "nutritively effective" amount as required by Applicants' claims. As noted above, "nutritively effective amount" is defined in Applicants' specification and claims as providing concentrations of nutrients that are at least the same "as that typically used for parenteral feeding and the rate of administration is at least the same but preferably higher than typically prescribed such as preferably a rate providing up to 1000 g of glucose or its equivalent per patient per day." (Spec. p. 3, lines 25-29; claims 1, 44, and 51). In comparison, Habener only discloses the use of carbohydrates and other compounds in amounts sufficient to prepare its described controlled release dosage forms, and not in amounts that would be considered "nutritively effective". This conclusion is supported by Habener's own teachings that such peptides, carbohydrates, glycosylated peptides, lipids, etc. constitute "contaminants" from which the GLP-1 derivatives should be substantially free. Certainly, a person skilled in the pharmaceutical arts would not reasonably conclude that Habener's disclosed compounds for use in preparing certain controlled release dosage forms would be present in the Habener compositions in an amount "typically used for parenteral feeding" as required by Applicants' claims.

Since Habener '492 does not teach parenteral administration of insulinotropic peptides in combination with one or more nutrients as required by Applicants' claims, claims 1-2, 17-19, 20-25, 32-35, and 41-51 are not anticipated by Habener '492. Applicants therefore respectfully request that this ground of rejection be withdrawn.

III. Claim Rejections - 35 U.S.C. § 103

Claims 1-2, 17-25, 32-35, and 41-50 were rejected under 35 U.S.C. § 103(a) as being unpatentable over the Specification disclosure as to the state of the prior art in view of Habener '492 and/or Eng U.S. Pat. No. 5,424,286 ("Eng '286"). Applicants respectfully traverse this rejection.

The PTO bears the burden of establishing a case of prima facie obviousness. In re Fine, 837 F.2d 1071, 1074 (Fed. Cir. 1988). The critical inquiry for obviousness is whether "there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination." Fromson v. Advance Offset Plate, Inc., 755 F.2d 1549, 1558 (Fed. Cir. 1985). In other words, obviousness "cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination." In re Fine, 837 F.2d 1071, 1075 (Fed. Cir. 1988), quoting ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577 (Fed. Cir. 1984). This suggestion cannot stem from the applicant's own disclosure, however. In re Ehrreich, 590 F.2d 902 (CCPA 1979).

The Examiner admits that the state of the prior art as described in the specification differs from the presently claimed invention which incorporates the use of insulinotropic peptides in parenteral nutrition compositions which comprise nutrients for alimentary nutrition or to treat hyperglycemic states. However, Habener and Eng, even in combination, still fail to provide these missing teachings of the claimed invention.

As already noted above, Habener's disclosed methods are directed only towards treating patients with diabetes or hyperglycemia for purposes of lowering their plasma glucose levels. Similarly, Eng '286 teaches the administration of insulinotropic compounds only for purposes of treating diabetes mellitus and in the prevention of hyperglycemia. (See Abstract; Col. 2, lines

36-40). Neither Habener nor Eng teaches or suggests the use of GLP-1 or its derivatives for other purposes, and certainly not for Applicants' methods of non-alimentary nutrition and enhancing metabolism of nutrients as set forth in claims 1-2, 17-19, 20-25, 32-35, 41, 42, 44, and 51. Therefore, these claims are not rendered obvious by the Specification in view of Habener and/or Eng.

Again, the Examiner argues that Habener's "meal studies" as described in Example 11 meet the requirements of Applicants' claims which describe the co-administration of insulinotropic peptides along with nutrients. However, as already noted, the Habener meal studies are only directed to the treatment of diabetic patients. (Col. 26, lines 19-23). Similarly, Eng teaches the infusion of GLIP along with meals only for purposes of lowering blood glucose concentration, and not in a method of non-alimentary nutrition or for enhancing metabolism of nutrients as set forth in Applicants' claims. (Col. 1, lines 59-62).

Since the prior art of record does not teach or suggest a method of using insulinotropic peptides for any purpose other than decreasing plasma glucose levels, it does not render claims 1-2, 17-19, 20-25, 32-35, 41, 42, 44, and 51 obvious.

In addition, the prior art of record fails to teach the co-administration of an insulinotropic peptide and a nutrient in a "nutritively effective amount". As already shown above, Habener '492 does not teach or suggest the inclusion of carbohydrates and other compounds in its compositions in a "nutritively effective" amount as required by Applicants' claims. This amount is defined as providing concentrations of nutrients that are at least the same "as that typically used for parenteral feeding and the rate of administration is at least the same but preferably higher than typically prescribed such as preferably a rate providing up to 1000 g of glucose or its equivalent per patient per day." (Spec. p. 3, lines 25-29; claims 1, 44, and 51). Habener, however, only discloses the use of carbohydrates and other compounds in amounts sufficient to prepare his described controlled release dosage forms, and not in amounts that would be considered "nutritively effective", i.e. in an amount "typically used for parenteral feeding". This conclusion is supported by Habener's own teachings that such peptides, carbohydrates, glycosylated

peptides, lipids, etc. constitute "contaminants" from which the GLP-1 derivatives should be substantially free. (Col. 9, lines 16-26).

The Examiner argues that "[t]he determination of optimal amounts of "insulinotropic" peptides and/or nutrients taken sequentially or in combination is well within the skill of the art as well as the determination of optimal delivery formulations (e.g. tablets, pills, delayed release etc.) and time of delivery (e.g. coadministered, sequential etc.)." In view of the prior art of record, Applicants respectfully disagree. The cited references do not teach the inclusion of Applicants' disclosed nutritive components in a "nutritively effective amount" as required by Applicants' claims. In fact, Habener specifically teaches away from the inclusion of these components in his teaching that such compounds constitute "contaminants".

While Habener discloses the use of carbohydrates and other compounds for use in the manufacture of particular dosage forms for administration of his GLP-1 derivatives, there would be no incentive or motivation for a person skilled in the art to increase the concentration of these compounds to the levels claimed by Applicants. Specifically, since Habener does not teach the use of these compounds for any purpose other than formulating controlled release dosage forms, a person skilled in the art would not be inclined to add additional carbohydrates, polyamino acids, etc. since to do so would "contaminate" the Habener GLP compositions. Eng '286 also fails to provide this missing teaching or suggestion of the administration of a nutritively effective composition comprising an insulinotropic compound in combination with one or more nutrients.

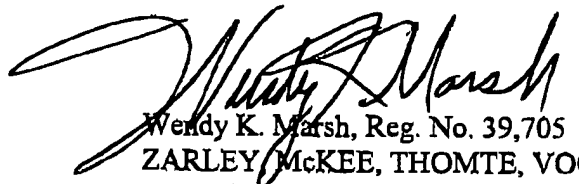
Since the prior art of record does not teach or suggest parenteral administration of insulinotropic peptides in combination with one or more nutrients in a nutritively effective amount as required by Applicants' claims, claims 1-2, 17-19, 20-25, 32-35, and 41-51 are not rendered obvious by the Specification in view of Habener and/or Eng. Applicants therefore respectfully request that this ground of rejection be withdrawn.

IV. Conclusion

For the above-stated reasons, it is submitted that the claims are in a condition for allowability. Applicants respectfully request allowance of the application.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,



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Application No. 09/011,940

AMENDMENT — VERSION WITH MARKINGS TO SHOW CHANGES MADE — DO NOT FILE

In the Claims

Claims 1, 2, 20-22, 41-42, and 44 have been amended as follows:

1. (Thrice Amended)

A method for non-alimentary nutrition comprising administering by a parenteral route to a patient in need of parenteral nutrition, a nutritively effective amount of [composition comprising] one or more nutrients selected from the group consisting of carbohydrates, amino acids, lipids, free fatty acids, mono-or diglycerides, glycerol [or] and any combination thereof; and one or more insulinotropic peptides, wherein the insulinotropic peptide is GLP-1, GIP, GLP-1 (7-34), GLP-1 (7-35), GLP-1 (7-36), GLP (7-37), the deletion sequences thereof, the natural and non-natural amino acid residue substitutes thereof, the C-terminus carboxamides thereof, the C-terminus esters thereof, the D-terminus ketones thereof, the N-terminus modifications thereof, or any mixture thereof, wherein the administration of the nutrient(s) produces a blood glucose level in the patient of from about 80 to 180 mg glucose per deciliter of blood, and the rate of administration is calculated to deliver up to about 1000 g of glucose or its equivalent per patient per day.

Claims 2 and 20 have been canceled.

21. (Thrice Amended)

The method of claim 1 wherein the insulinotropic peptide or peptides are administered by infusion at a rate of 0.01 to 50 pmol per kg of body weight of patient per minute.

Claim 22 has been canceled.

41. (Thrice Amended)

A method of enhancing metabolism of nutrients, comprising administering by a parenteral route to a non-diabetic patient in need of enhancing metabolism of nutrients a nutritively effective [composition comprising] amount of one or more nutrients or any combination thereof and one or more insulinotropic peptide or peptides, wherein said peptide or peptides is GLP-1, GLP-1 (7-34), GLP-1 (7-35), GLP-1 (7-36), GLP (7-37), the deletion sequences thereof, the natural and non-natural amino acid residue substitutes thereof, the C-terminus carboxamides thereof, the C-terminus esters thereof, the D-terminus ketones thereof, the N-terminus modifications thereof, or any mixture thereof.

42. (Twice Amended)

A method of enhancing metabolism of nutrients, comprising administering by a parenteral route to a patient with a disturbed glucose metabolism, a surgery patient, a comatose patient, a patient in shock, a patient with gastrointestinal disease, a patient with digestive hormone disease, an obese patient, an atherosclerotic patient, a patient with vascular disease, a patient with gestational diabetes, a patient with liver disease, a patient with liver cirrhosis, a patient with glucocorticoid excess, a patient with Cushings disease, a patient with activated

counterregulatory hormones that occur after trauma or a disease, a patient with hypertriglyceridemia, or a patient with chronic pancreatitis, a nutritively effective [composition comprising] amount of one or more nutrients or any combination thereof and one or more insulinotropic peptides.

44. (Thrice Amended)

A method of enhancing metabolism of nutrients, comprising administering by a parenteral route to a patient in need of enhancing metabolism of nutrients a nutritively effective [composition comprising] amount of glucose and one or more insulinotropic peptide or peptides, wherein said insulinotropic peptide or peptides is GLP-1, GLP-1 (7-34), GLP-1 (7-35), GLP-1 (7-36), GLP (7-37), the deletion sequences thereof, the natural and non-natural amino acid residue substitutes thereof, the C-terminus carboxamides thereof, the C-terminus esters thereof, the D-terminus ketones thereof, the N-terminus modifications thereof, or any mixture thereof; wherein the administration of the nutrient(s) produces a blood glucose level in the patient of from about 80 to 180 mg glucose per deciliter of blood, and the rate of administration is calculated to deliver up to about 1000 g of glucose or its equivalent per patient per day.

New claim 51 was added:

51. (New)

A method for non-alimentary nutrition comprising administering by a parenteral route to a patient in need of parenteral nutrition, a nutritively effective amount of one or more nutrients selected from the group consisting of carbohydrates, amino acids, lipids, free fatty acids, mono-or

diglycerides, glycerol and any combination thereof; and one or more insulinotropic peptides, wherein the insulinotropic peptide is GLP-1, wherein the administration of the nutrient(s) produces a blood glucose level in the patient of from about 80 to 180 mg glucose per deciliter of blood, and the rate of administration is calculated to deliver up to about 1000 g of glucose or its equivalent per patient per day.